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The Standard of Quality℠

Sally Seaver, Chair
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United States Pharmcopeia

I would like to thank the Office of Ombudsman at the FDA for the opportunity to speak at this hearing. I am speaking today in my role as Chair of the United States Pharmacopeia's Expert Committee on Gene Therapy, Cell Therapy, and Tissue Engineering. This presentation is based on this committee's past work, which culminated in the information chapter <1046> *Cell and Gene Therapy Products*, its current work on an information chapter *on Ancillary Products for Cell and Gene Therapy Products*, and its work with companies in writing monographs for wound healing products that contain live cells.

It is not the committee's intention today to testify as to which Center in the FDA should have jurisdiction over these products or on the primary mechanism of action of these products. Our work has always assumed that reproducibly in manufacturing a safe product with live, functioning cells was the goal. I intend to focus today on our work to provide information for cell and gene therapy products in general, and monographs and reference standards for wound healing products with live cells, in particular.

The forerunner of this Expert Committee was an advisory group to the USP Subcommittee on Biotechnology and Gene Therapy that was formed in December, 1997. This group was composed of scientists and clinicians from academic medical centers, the biopharmaceutical industry, both large and small, and the government, including the FDA. The members have experience with cell based products for wound healing, bone marrow transplantation, xenogeneic cell therapies, patient specific cell therapies, and viral and non-viral gene therapies, as well as traditional biotechnology-derived products. At that December 1997 meeting the group decided that we would write an informational chapter on cell and gene therapies, after which we could focus work on the issue of ancillary products for these products. The goal of this first chapter, <1046> *Cell and Gene Therapy Products*, was "to summarize the issues and best current practices in the manufacturing, testing and administration of cell and gene therapy products." In other words, we wanted the chapter

- to contain all of the information the Committee would have liked to have known if they were starting out in these fields today,
- to cite examples that are directly relevant to those making cell and gene therapy products,
- to look forward towards the standards and practices for approved products, but
- to present also general information on the development, manufacturing and testing of these products.

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Since this is a new field, we considered the relevance of all regulatory guidances, whether or not they specifically were devised for these products. These included the numerous CBER Points to Consider and Guidances, the ICH Guidelines, especially those for biotechnology-derived products, 21 CFR 210, 211, 600s, and 820, the Quality Systems Regulations (QSR), and ISO guidances. We were influenced by aspects from all of these sources. In fact, an overriding theme of this Chapter is that the ICH Guidelines, especially those for biotechnology-derived products, are useful in that principles of these guidelines can be applied to cell and gene therapy products, even if the guidelines specifically state that they are not applicable to cell and gene therapy. To help apply the important principles of these guidelines, guidances, and regulations the panel tried to provide useful examples that are specific to cell and gene therapy. The goal with these examples is to go beyond the FDA definitions and guidances to make these guidances relevant to the field of cell and gene therapy.

A complete outline of <1046> is attached. I will highlight only those sections that are relevant for wound healing products containing live cells. We divided manufacturing into multiple sections. The first section is a manufacturing overview. It discusses raw materials sourcing and qualification, characterization of cell and virus banks, in process controls, specifications and considerations for validation. This section was strongly influenced by the risk assessment and design approaches of QSR, by the numerous CBER points to consider, and guidances on testing these products for adventitious agents. The manufacturing of cell therapy product section contains much information that is directly relevant to this type of wound healing product, including a concise list of the desired qualities for the supporting matrix. We felt that any preparation of the final product done at the clinical site should be viewed as an extension of manufacturing and should be supported by appropriate SOPs and facilities, and by people trained in the processing. We organized the analytical methodologies section so that safety was the first item detailed, not the last. In addition, these products need assays for defining the dose, potency, purity, and identity of the product. The stability section points out that brief excursion in temperature to outside the stated limits, such as may occur in an airplane hold or in a surgical suite, may be as damaging as a long term exposure to conditions just outside storage specifications. The storage and shipping section discusses issues both with storing a product frozen as well as with shipping it in an unfrozen form. The chapter concludes with brief sections on labeling these products, on regulations, standards, and new methodologies for these products, and a list of definitions and abbreviations.

An initial draft of <1046> was published in the January-February 2000 issue of *Pharmacopeial Forum* for public comments. About 500 copies were distributed to interested parties, mainly practitioners. A revised version was published in the January-February 2001 issue of *PF*. Based on a few additional comments, a final version of

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<1046> was approved by the Expert Committee and published as part of the *First Supplement* to *USP 25/NF 20*, which became effective April 1, 2002.

In 2000, the Expert Committee also started work on a second information chapter that discusses sourcing and qualifying ancillary products for use in the manufacturing of cell and gene therapy products. Ancillary products are those materials used in the manufacturing of the therapeutic product that are not intended to be in the final product. Again, the Committee has found CBER's extensive guidances on adventitious agents and handling of biotechnology derived products to be important. We also find CDRH's QSR approach extremely helpful. The QSR spell out a more comprehensive approach to quality than CBER's specification for the quality function. QSR starts right at the conceptualization, design and development phases (design controls), and directly addresses risk assessment for products and raw materials. Addressing these issues upfront is important for developing a manufacturing process to produce safe cell or gene therapy products that consistently demonstrate the expected activity.

More recently, the Expert Committee has worked with three companies on monographs for wound healing products containing live cells. A draft monograph for one of these products was published in the November-December 2001 issue of *PF*. The other two monographs are still in an early stage of development. Each monograph contains sections that describe (a) the product configuration, adventitious agents, and other non-USP specified testing, (b) packaging and storage, (c) labeling, (d) USP Reference Standard, and (e) tests to identify the product. The Committee would like to emphasize that in the USP tradition these tests are not intended to be routine release tests for these products, but are a set of tests that can be used to distinguish these cellular products from each other, from other wound healing products, and that would ensure the consistent quality of these products. These three wound healing products are all clearly different from each other.

After working on its first monograph, the committee decided that monographs for wound healing products containing live cells should include the following for types of tests.

1. Detailed histology of the product that clearly demonstrates the organization of the different cell types relative to the matrix, as well as the gross structural properties of the matrix.

2. Test(s) to identify the different cell types and the matrix.

3. Test(s) that show the cells to be viable or to have the expected metabolic activity in the final product.

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4. Test(s) for other unique properties, if relevant. For instance, in the draft monograph published last fall, there is an assay that demonstrates that the top layer of that particular wound healing product with live cells was cornified.

The Reference Standard for that monograph is a series of photomicrographs of the histology of the product that depict product that passes these monograph specifications, as well as product that fails these specifications. These photomicrographs are in the process of being reviewed by independent pathologists for their acceptability as a Reference Standard.

The Committee urges that all wound healing products with live cells be reviewed by the same FDA Center so there is consistency of review. The Committee members urge that the chosen Center be versed in both relevant issues with live cell products, as well as issues with biomaterials and their sourcing, and with ancillary products needed to make these cell products. They also feel that if the Center jurisdiction changes, there should be no undue regulatory burden placed on the manufacturers of the wound healing products already on the market, as it is the Committee's perception that there have been no major safety issues with these approved products. Finally, the Committee thanks both CBER and CDRH for the good relationships it has with them, and looks forward to working with whatever Center is chosen to regulate wound healing products with live cellular components.

Wound Healing Products with Live Cells

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<1046> Cell and Gene Therapy Products

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- Chapter Purpose and Organization

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IX. Regulations, Standards, and New Methodologies
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- Need for New Methodologies

X. Definitions of Terms

XI. Abbreviations

Monograph for Wound Healing Products with Live Cells

- Description, General Characteristics & Adventitious Agent Testing
- Packaging and Storage
- Labeling
- USP Reference Standard
- Tests
  - Histological characterization
  - Cell and matrix identity
  - Cell viability/metabolic function
  - Other unique characteristics